

Prurigo Pigmentosa Induced by Ketosis: Resolution Through Dietary Modification

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PRACTICE POINTS

- Ketosis can be associated with a specific rash known as prurigo pigmentosa (PP).
- Resolution of PP is related to re-introduction of carbohydrates into the diet.
- Consider asking about dietary modifications in patients presenting with a new rash.

To the Editor:

A 40-year-old white woman presented with a waxing and waning erythematous pruritic rash on the chest, back, and axillae of 3 years' duration. The appearance of the rash coincided with an intentional weight loss of more than 100 lb, achieved through various diets, most recently a Paleolithic (paleo) diet that was high in protein; low in carbohydrates; and specifically restricted dairy, cereal grains, refined sugars, processed foods, white potatoes, salt, refined oils, and legumes.¹ The patient had been monitoring blood glucose and ketone levels. Prior to presentation, she received various treatments including clotrimazole cream and topical steroids with no improvement.

On physical examination, there were scaly, pink-red, reticulated papules and plaques coexisting with tan reticulated patches that were symmetrically distributed on the central back, lateral and central chest (Figure 1A), breasts, and inframammary areas. During the most severe flare-up, the blood ketones measured 1 mmol/L. There was no relevant medical history. She was of Spanish and Italian descent.

Histologic sections showed a sparse infiltrate of lymphocytes surrounding superficial dermal vessels and a mildly acanthotic epidermis with a focally parakeratotic stratum corneum (Figure 2A). Pigmentary incontinence and subtle interface changes were apparent, including rare necrotic keratinocytes (Figure 2B). No eosinophils or neutrophils were present.

After the initial presentation, carbohydrates were added back into her diet and both the ketosis and eruption remarkably resolved. When carbohydrate restriction was rechallenged, she again entered ketosis (0.5 mmol/L), followed by subsequent recurrence of the pruritic lesions. With re-introduction of carbohydrates, the eruption and ketosis once more resolved, leaving only postinflammatory reticulated hyperpigmentation (Figure 1B). Based on the clinical presentation, supportive histopathologic findings, and interesting response to ketones and diet modification, the patient was diagnosed with prurigo pigmentosa (PP).

Prurigo pigmentosa is a rare inflammatory dermatosis that was initially described in 1971 as "a peculiar pruriginous dermatosis with gross reticular pigmentation" by Nagashima et al.² Prurigo pigmentosa is most frequently diagnosed in Japan, and since its discovery, it has been reported in more than 300 cases worldwide.²⁻⁴

Fewer than 50 non-Japanese cases have been reported, with the possibility of an additional ethnic predisposition among the Turkish and Sicilian populations, though only 6 cases have been reported in the United States.³⁻⁶ Prurigo pigmentosa tends to occur in the spring and summer months and is most common among young females, with a mean age of 24 years. The typical lesions of PP are symmetrically distributed on the trunk with a tendency to localize on the upper back, nape of the neck,

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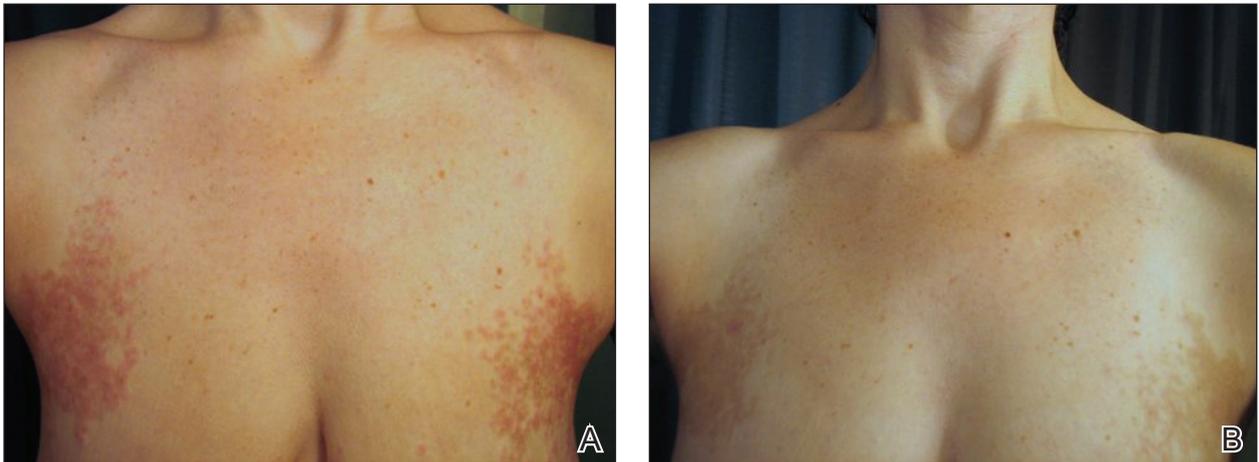


FIGURE 1. A, Scaly pink-red papules coalesced into reticulated plaques with coexisting reticulated hyperpigmentation on the lateral chest and breasts. B, Erythematous plaques resolved after diet modification and normalization of ketones. Reticulated hyperpigmentation remained.

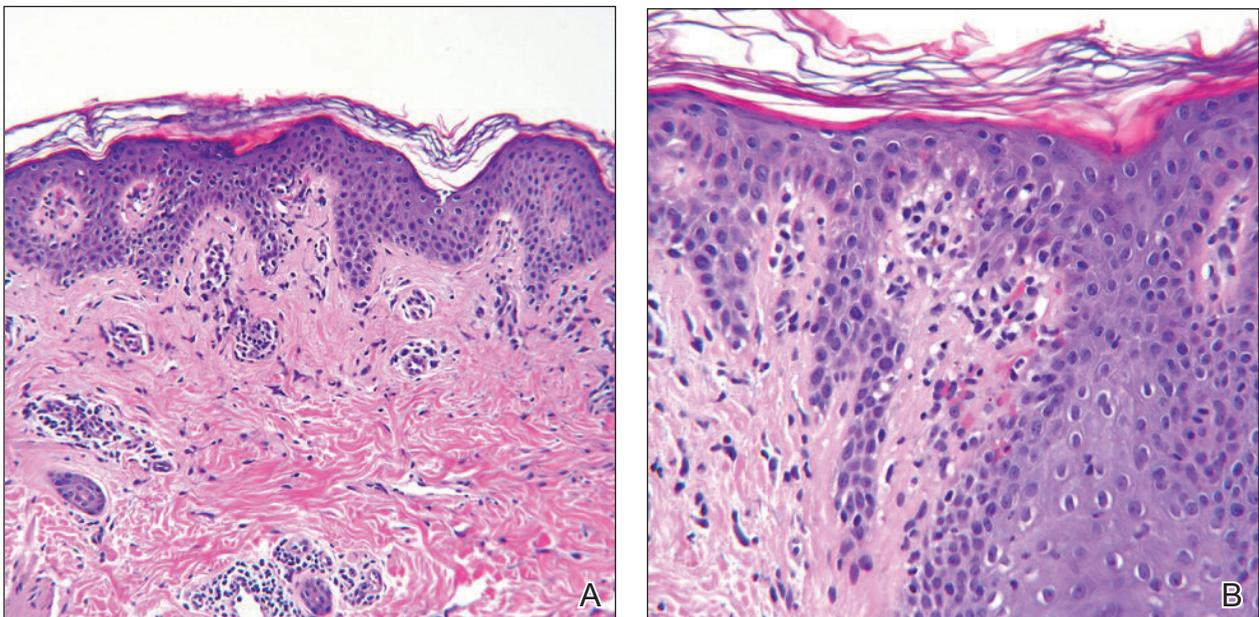


FIGURE 2. A, Histopathology showed a lymphocytic perivascular infiltrate within the superficial dermis as well as an acanthotic and parakeratotic epidermis (H&E, original magnification $\times 100$). B, Pigmentary incontinence and subtle interface changes were apparent, including rare necrotic keratinocytes (H&E, original magnification $\times 200$).

and intermammary and inframammary regions. Eruptions have been reported to occur on additional areas; however, mucous membranes are always spared.⁶

Individual lesions differ in appearance depending on the stage of presentation and are categorized as early, fully developed, resolving, and late lesions.⁶ Pruritic macules and papules are present early in the disease state and resolve into crusted and/or scaly papules followed by pigmented macules. Early lesions tend to be intensely pruritic with signs of excoriation, while resolving lesions lack symptoms. Lesions last approximately 1 week but tend to reappear at the site where they were previously present, which allows for lesions of different ages to

coexist, appearing in a reticular arrangement with hyperpigmented mottling lasting from a few weeks to months.⁶

Just as the clinical picture transpires rapidly within 1 week, so do the histopathologic findings.⁶ Early lesions are categorized by a superficial perivascular and interstitial infiltrate of neutrophils, spongiosis, ballooning, and necrotic keratinocytes. These early lesions are present for less than 48 hours, and these histopathologic findings are diagnostic of PP. Within 2 days, lymphocytes predominate in the dermal infiltrate, and a patchy lichenoid aspect is established in the fully developed lesion along with reticular and vacuolar alterations. Late lesions show a parakeratotic and hyperpigmented epidermis with

melanophages present in the papillary and reticular dermis. At this last stage, the histopathologic features of PP are indistinguishable from any other disease that results in postinflammatory hyperpigmentation, making diagnosis difficult.⁶

A variety of therapeutic options are used in the treatment of PP, with the most effective agents being oral antibiotics including dapsone, minocycline, and doxycycline, all of which limit the local tissue inflammatory response and cytotoxic effects. Topical and systemic antihistamines as well as corticosteroids are ineffective and have not been shown to prevent the postinflammatory reticular pigmentation.⁶⁻¹⁰

Various underlying factors have been associated with PP, including friction, heat, sunlight, sweating, allergic contact sensitization, and ketosis due to nutritional deficiency or diabetes mellitus; however, the exact etiology remains ambiguous.²⁻⁷ The association with ketosis and nutrition is of particular interest in this case. Onset of PP has been reported to coincide with dieting, fasting, weight loss, anorexia nervosa, and diabetes mellitus.^{3,6-9} Roughly 50 patients with PP had ketosis subsequent to these metabolic disturbances.^{3,6-10} As of now, the only reported correlation between ketosis and PP is that upon diet modification, lesions resolved following ketone normalization, as was observed in our patient.^{3,6-8} Reports of PP in diabetic patients while in ketoacidosis describe resolution of lesions with insulin administration.⁶⁻⁹ The pathophysiology of ketosis and its association with PP is unclear; however, the similarities seen in the immune response of PP and that stimulated by ketosis may expose an associated mechanism.

Ketosis is a temporary condition characterized by elevated serum ketones that are used as an alternative energy source when blood glucose is low or insulin is deficient.¹¹ The most common causes of ketosis are the physiologic responses to fasting, prolonged exercise, or a high-protein/low-carbohydrate diet, though pathologic causes include insulin-dependent diabetes mellitus, alcoholism, and salicylate overdose.¹¹ In healthy individuals, blood ketone levels rarely approach 0.5 mmol/L. Prolonged fasting or restricting intake of carbohydrates to less than 40 g daily can induce mild ketosis that resolves with re-introduction of carbohydrates.¹¹

Ketone bodies pass from the circulating blood into tissues or remain near the blood vessels, inducing cytotoxic effects and perivascular inflammation.^{10,11} Increased ketone bodies have been shown to upregulate intercellular adhesion molecule 1 (ICAM-1) and leukocyte function-associated antigen 1 (LFA-1), a phenomenon also seen in lesional keratinocytes of PP.^{12,13} Teraki et al¹³ observed that epidermal keratinocytes exhibited increased expression of ICAM-1 as well as intense expression of LFA-1 on dermal and epidermotropic leukocytes, which was thought to be due to cell-mediated cytotoxicity. Not only do increased ketone bodies upregulate ICAM-1 and LFA-1, but they also are involved in increasing many

proinflammatory mediators that may be capable of inducing the response seen in PP keratinocytes.^{12,13}

Intercellular adhesion molecule 1 is important in initiating cellular interactions in the immune response and is the ligand for LFA-1 found on most leukocytes.¹⁴ Increased ICAM-1/LFA-1 interaction is thought to be the major pathway by which leukocytes are able to attach to keratinocytes and endothelial cells, allowing for leukocyte tissue migration and specific immunologic reactions, including leukocyte-mediated cytotoxicity. Interestingly, glucocorticoids are ineffective in reducing the expression of ICAM-1 in cultured keratinocytes.¹⁴ This connection between ketosis and inflammation that results in leukocyte migration and ultimately keratinocyte cytotoxicity may well be fundamental to the pathophysiology of PP and may provide a possible explanation for the ineffectiveness of corticosteroid treatment.

Middleton and Norris¹⁵ observed that individual keratinocyte strains show considerable variability in ICAM-1 expression that was found to be attributable to genetic polymorphisms. The presence of a particular polymorphism affecting ICAM-1 expression on human keratinocytes may explain the apparent ethnogeographic predisposition of PP as well as the ease at which ICAM-1 is expressed in the presence of ketones.

We describe a case of a 40-year-old white woman who was diagnosed with PP that was prompted by a 100-lb weight loss and self-induced ketosis while following a paleo diet with carbohydrate restriction. Successful treatment was attained through diet modification alone. This interesting case was another instance in which the pathophysiology of PP was attributed to ketosis. Because not all patients that are in ketosis have PP, larger prospective cohort studies are needed to further elucidate the association of PP and ketosis.

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